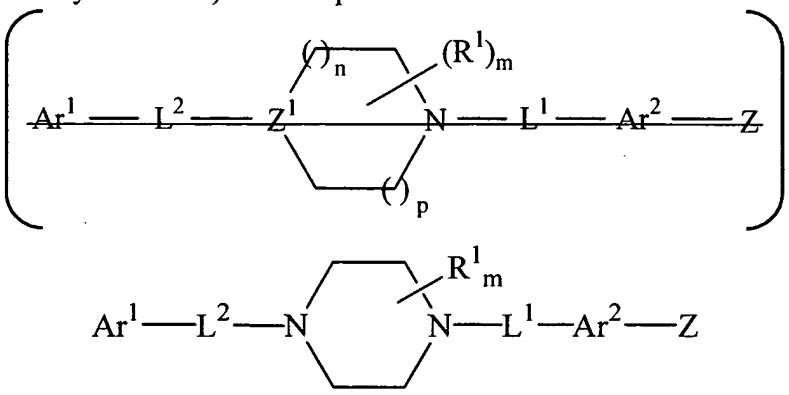
CLAIM AMENDMENTS

1. (currently amended): A compound of the formula:



[[~~and~~]] or the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein:

Ar^1 is an aryl group substituted with 0-5 non-interfering substituents, wherein two adjacent noninterfering substituents can form a fused aromatic or nonaromatic ring;

L^1 and L^2 are linkers;

each R^1 is independently a noninterfering substituent;

~~Z^1 is CR^2 or N wherein R^2 is hydrogen or a noninterfering substituent;~~

m is 0-4;

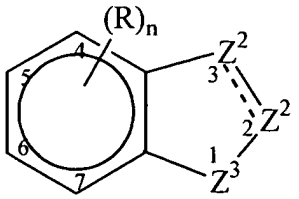
~~each of n and p is an integer from 0-2 wherein the sum of n and p is 0-3;~~

Ar^2 is a substantially planar, monocyclic or polycyclic aromatic moiety having one or more optional ring heteroatoms, said moiety being optionally substituted with one or more non-interfering substituents, two or more of which may form a fused ring;

Z is $-W_i-COX_jY$ wherein Y is COR^3 or an isostere thereof; R^3 is a H or a noninterfering substituent, each of W and X is a spacer of 2-6 Å, and each of i and j is independently 0 or 1;

~~wherein the smallest number of covalent bonds in the compound separating the atom of Ar^1 bonded to L^2 to the atom of Ar^2 bonded to L^1 is at least 6, where each of said bonds has a bond length of 1.2 to 2.0 angstroms; and/or~~ wherein the distance in space between the atom of Ar^1 bonded to L^2 and the atom of Ar^2 bonded to L^1 is ~~4.5-24angstroms;~~ is no more than 24 angstroms;

with the proviso that the portion of the compound represented by Ar^2-Z is not



wherein ⚌ represents a single or double bond; n is 0-3; one Z^2 is CA or CRA and the other is CR, CR_2, NR or N; A is $-W_i-COX_jY$ wherein Y is COR or an isostere thereof, each of W and X is a spacer of 2-6Å, and each of i and j is independently 0 or 1; Z^3 is NR or O; and each R is independently hydrogen or a noninterfering substituent.

2. (canceled)

3. (original): The compound of claim 1 wherein Z is $COXjCOR^3$, and

wherein R^3 is H, or is straight or branched chain alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, or heteroarylalkyl, each optionally substituted with halo, alkyl, heteroalkyl, SR, SOR, SO_2R, SO_2NR_2, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, CN, COOR, $CONR_2$, COR, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, or

wherein R^3 is OR, NR_2, SR, $NRCONR_2$, $OCONR_2$, or $NRSO_2NR_2$, wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, and wherein two R attached to the same atom may form a 3-8 member carbocyclic or heterocyclic ring and wherein said ring may further be substituted by alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, each optionally substituted with halo, SR, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof wherein two R attached to the same atom may form a 3-8 member ring, optionally substituted as above defined; and

X, if present, is CR_2 where R is as defined above.

4. (original): The compound of claim 1 wherein Y is an isostere of COR^3.

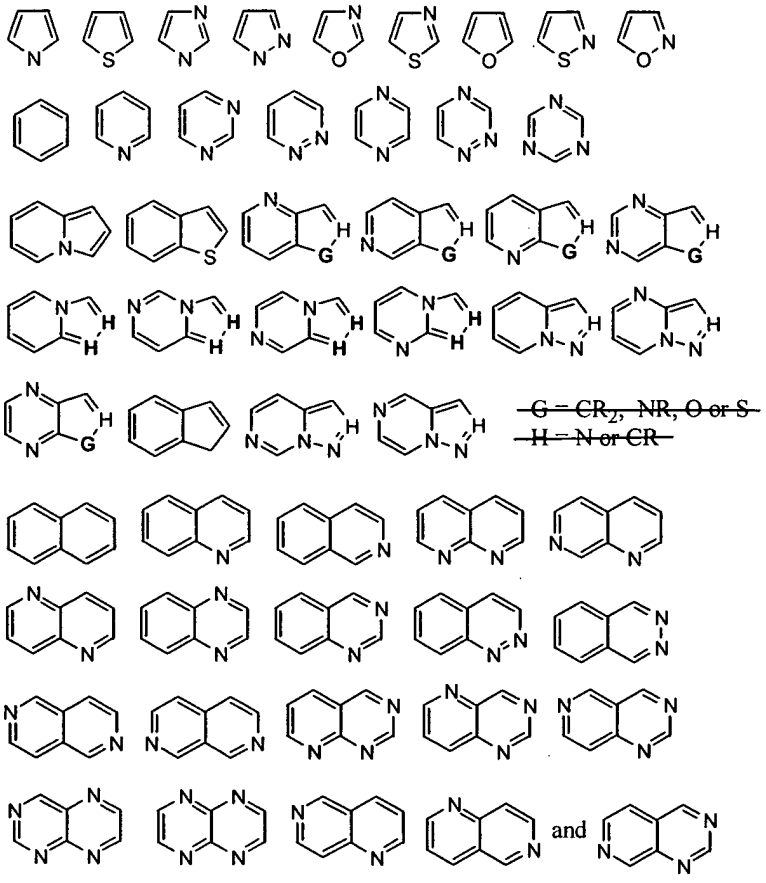
5. (original): The compound of claim 4 wherein Y is tetrazole; 1,2,3-triazole; 1,2,4-triazole; or imidazole.

6. (original): The compound of claim 1 wherein each of i and j is 0.

7. (original): The compound of claim 3 wherein j is 0.

8. (currently amended): The compound of claim 1 wherein $-Ar^2-$ comprises an optionally substituted monocyclic or polycyclic aromatic nucleus, wherein said aromatic nucleus consists of carbocyclic or heterocyclic ring selected from (i) a five-membered heterocyclic or carbocyclic ring; (ii) a six-membered carbocyclic or heterocyclic ring; (iii) a five-membered carbocyclic or ~~heterocycloc~~ heterocyclic ring fused to another five-membered carbocyclic or heterocyclic ring; (iv) a six-membered carbocyclic or heterocyclic ring fused to another six-membered carbocyclic or heterocyclic ring; and (v) a five-membered heterocyclic or carbocyclic ring fused to a six-membered carbocyclic or heterocyclic ring.

9. (currently amended): The compound of claim 8 wherein Ar^2 is selected from:

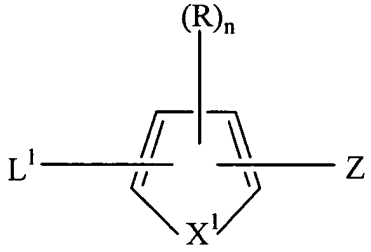


<u>wherein G is CR_2, NR, O or S; and</u>

<u>H is N or CR</u>

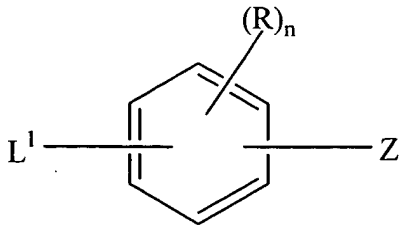
[[~~where~~**]]** <u>wherein</u> R is <u>hydrogen or</u> a noninterfering substituent.

10. (currently amended): The compound of claim 8 wherein the portion of said compound represented by L^1-Ar^2-Z is selected from the following:



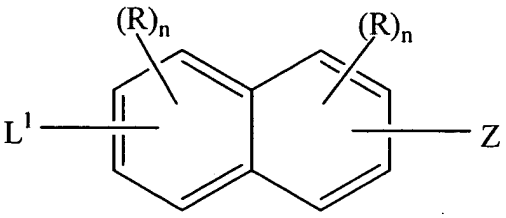
(I)

wherein n is 0, 1 or 2; X^1 is NR, CR_2, O or S; and each R is independently H or a noninterfering substituent; and two or more R groups may form a fused ring;



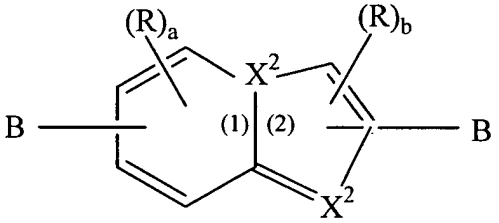
(II)

wherein n is 0-4; R is H or a noninterfering substituent where two or more R groups may form a fused ring; and one or more ring carbons may be optionally replaced with nitrogen;



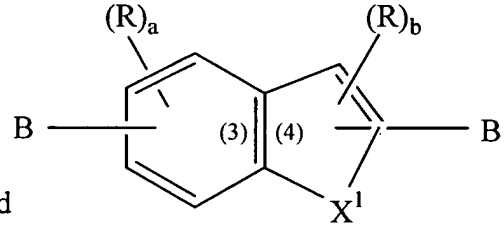
(III)

wherein each n is ~~inpendently~~ independently 0 to 3; R is H or a noninterfering substituent, where two or more R groups may form a fused ring; and one or more ring carbons may be optionally replaced with nitrogen;



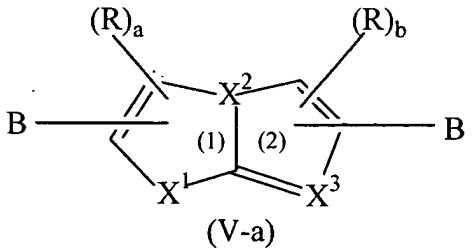
(IV-a)

and



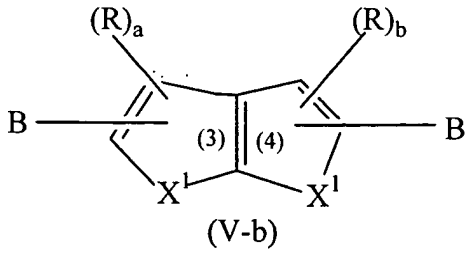
(IV-b)

wherein, subject to the proviso of claim 1, one B is L^1 and the other is Z; wherein a is 0 to 4 such that the positions on the six membered rings (1) and (3) to which $(R)_a$ is bonded can include X^2 when X^2 is C; b is 0–3 such that the positions on the five-membered rings (2) and (4) to which $(R)_b$ is bonded can include X^2 and X^1, when X^2 is C and X^1 is N or C; each X^2 is independently N or CR; X^1 is NR, CR_2, O or S; each R is H or a noninterfering substituent where two or more R groups may form a fused ring; wherein one or more of the ring carbons that are at positions other than X^2 or X^1 and that are also not bound to B can be optionally replaced with N;



(V-a)

and



(V-b)

wherein one B is L^1 and the other is Z; a is 0-4 such that the positions on the rings (1) and (3) to which $(R)_a$ can be bonded include X^2 and X^1 where X^2 is C and X^1 is C or N; b is 0 or 3 such that the positions on the rings (2) and (4) to which $(R)_b$ can be bonded include X^1, X^2 and X^3 when X^1 is C or N and X^2 and/or X^3 are C; each X^1 is independently NR, $C(R)_2$, O or S; X^2 and X^3 are independently N or CR; each R is independently H or a noninterfering substituent where two or more R groups can optionally form a fused ring; wherein one or more of the ring carbons that are at positions other than X^1, X^2 or X^3, and that are also not bound to B, can be optionally replaced with N.

11. (original): The compound of claim 10 wherein L^1-Ar^2-Z is structure (I).

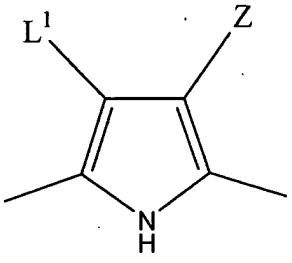
12. (original): The compound of claim 11 wherein X^1 in structure (I) is NR.

13. (original): The compound of claim 12 wherein X^1 in structure (I) is NH.

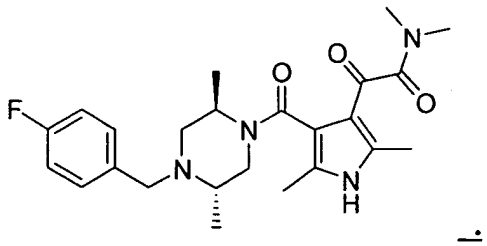
14. (original): The compound of claim 13 wherein R is methyl.

15. (original): The compound of claim 14 wherein n is 2.

16. (currently amended): The compound of claim 15 wherein structure (I) is:



17. (currently amended): The compound of claim 16 where the compound is:

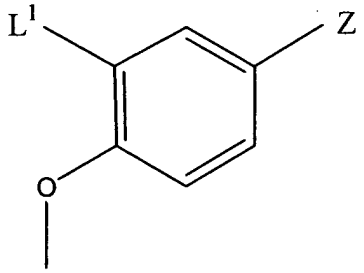


[[~~10~~]] 18. (currently amended): The compound of claim 10 wherein L^1-Ar^2-Z is structure (II).

19. (original): The compound of claim 18 wherein the R in structure (II) is methoxy.

20. (original): The compound of claim 19 wherein n in structure (II) is 1.

21. (currently amended): The compound of claim 20 wherein structure (II) is



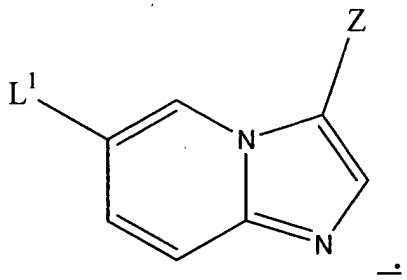
22. (canceled)

23. (original): The compound of claim 10 wherein L^1-Ar^2-Z is structure (III).

24. (original): The compound of claim 10 wherein L^1-Ar^2-Z is structure (IV-a) or (IV-b).

25. (original): The compound of claim 24 wherein L^1-Ar^2-Z is (IV-a) and both X^2 in structure (IV-a) are nitrogen.

26. (currently amended): The compound of claim 25 wherein structure (IV) is:



27. (canceled)

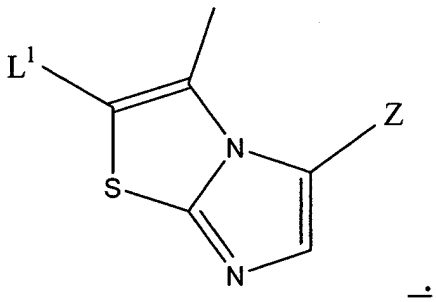
28. (original): The compound of claim 8 wherein L^1-Ar^2-Z is structure (V-a) or (V-b).

29. (original): The compound of claim 28 wherein L^1-Ar^2-Z is structure (V-a) and X^2 and X^3 in structure (V-a) are N.

30. (original): The compound of claim 29 wherein at least one R in structure (V) is methyl.

31. (original): The compound of claim 29 wherein X^1 in structure (V) is S.

32. (currently amended): The compound of claim 31 wherein structure (V) is:



33-34. (canceled)

35. (original): The compound of claim 1 wherein L^1 is CO, CHOH or CH_2.

36. (original): The compound of claim 35 wherein L^1 is CO.

37-38. (canceled)

39. (currently amended): The compound of claim 1 wherein L^2 is alkylene (1-4C) or alkenylene (1-4C) optionally substituted with a moiety selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, ~~alkyl-OOR~~ alkyl-OOCR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two substituents on L^2 can be joined to form a non-aromatic saturated or unsaturated ring that includes 0-3 heteroatoms which are O, S and/or N and which contains 3 to 8 members or said two substituents can be joined to form a carbonyl moiety or an oxime, oximeether, oximeester or ketal of said carbonyl moiety.

40. (original): The compound of claim 39 wherein L^2 is unsubstituted alkylene.

41. (original): The compound of claim 39 wherein L^2 is unsubstituted methylene, methylene substituted with alkyl, or -CH=.

42. (currently amended): The compound of claim 1 wherein Ar^1 is optionally substituted with 0-5 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, ~~alkyl-OOR~~ alkyl-OOCR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two of said optional substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.

43. (original): The compound of claim 42 wherein Ar^1 is optionally substituted phenyl.

44. (original): The compound of claim 43 wherein said optional substitution is by halo, OR, or alkyl.

45. (original): The compound of claim 44 wherein said phenyl is unsubstituted or has a single substituent.

46. (currently amended): The compound of claim 1 wherein R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, ~~alkyl-OOR~~ alkyl-OOCR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof and two of R^4 on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members, or R^4 is =O or an oxime, oximeether, oximeester or ketal thereof.

47. (original): The compound of claim 46 wherein each R^1 is halo, OR, or alkyl.

48. (original): The compound of claim 47 wherein m is 0, 1, or 2.

49. (original): The compound of claim 48 wherein m is 2 and both R^1 are alkyl.

50. (currently amended): The compound of claim 10 wherein each of the non-interfering groups R, when bonded to a ring carbon atom, are selected from the group consisting of:

(a) hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl and halo; or

(b) or from OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, ~~alkyl-OOR~~ alkyl-OOCR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R in the preceding (b) selections is independently H, alkyl, alkenyl or aryl or heteroforms thereof;

and wherein two of the non-interfering groups R can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.

51. (currently amended): The compound of claim 50 wherein the non-interfering groups R are independently selected from the group consisting of H, alkyl, acyl, aryl, arylalkyl, heteroalkyl, heteroaryl, halo, OR, NR_2, SR, NRCOR, ~~alkyl-OOR~~ alkyl-OOCR, RCO, COOR, and CN, wherein each R is independently H, alkyl, or aryl or heteroforms thereof.

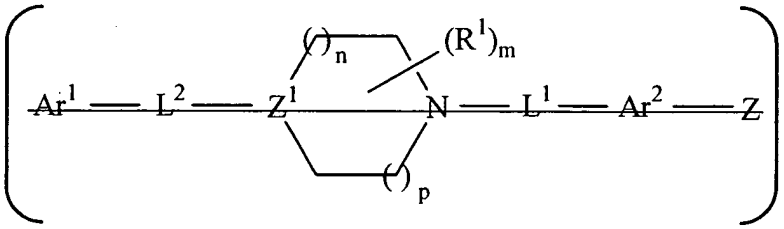
52. (original): The compound of claim 10 wherein the noninterfering groups R, when bonded to a nitrogen ring atom, are selected from the group consisting of:

(a) H, or alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl; and

(b) SOR, SO_2R, RCO, COOR, alkyl-COR, SO_3R, $CONR_2$, SO_2NR_2, CN, CF_3, or R_3Si wherein each R in the preceding (b) selections is independently H, alkyl, alkenyl or aryl or heteroforms thereof.

53. (currently amended): A pharmaceutical composition for treating conditions characterized by enhanced p38-α activity which composition comprises

a therapeutically effective amount of a compound of claim 1 ~~the formula~~



~~and the pharmaceutically acceptable salts thereof~~ along with a pharmaceutically acceptable excipient~~, or a pharmaceutical composition thereof, wherein:~~

~~Ar^1 is an aryl group substituted with 0-5 non-interfering substituents, wherein two adjacent noninterfering substituents can form a fused aromatic or nonaromatic ring;~~

~~L^1 and L^2 are linkers;~~

~~each R^1 is independently a noninterfering substituent;~~

~~Z^1 is CR^2 or N wherein R^2 is hydrogen or a noninterfering substituent;~~

~~m is 0-4;~~

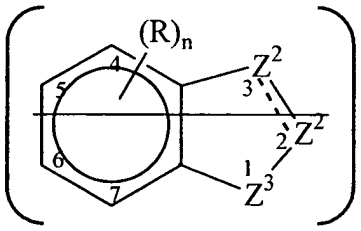
~~each of n and p is an integer from 0-2 wherein the sum of n and p is 0-3;~~

~~Ar^2 is a substantially planar, monocyclic or polycyclic aromatic moiety having one or more optional ring heteroatoms, said moiety being optionally substituted with one or more non-interfering substituents, two or more of which may form a fused ring;~~

~~Z is $-W_i-COX_jY$ wherein Y is COR^3 or an isostere thereof; R^3 is a noninterfering substituent, each of W and X is a spacer of 2-6 Å, and each of i and j is independently 0 or 1;~~

~~wherein the smallest number of covalent bonds in the compound separating the atom of Ar^1 bonded to L^2 to the atom of Ar^2 bonded to L^1 is at least 6, where each of said bonds has a bond length of 1.2 to 2.0 angstroms; and/or wherein the distance in space between the atom of Ar^1 bonded to L^2 and the atom of Ar^2 bonded to L^1 is 4.5-24 angstroms;~~

~~with the proviso that the portion of the compound represented by Ar^2-Z is not~~



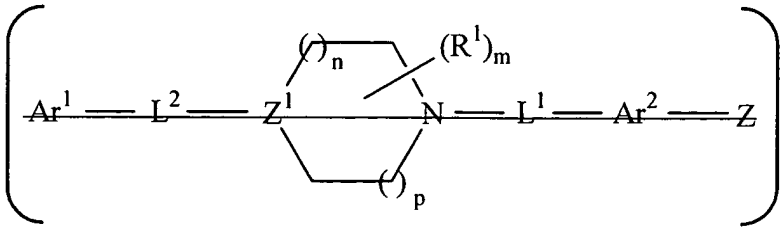
~~wherein ⫽ represents a single or double bond; n is 0-3; one Z^2 is CA or CRA and the other is CR, CR_2, NR or N; A is $-W_i-COX_jY$ wherein Y is COR or an isostere thereof, each of W and X is a spacer of 2-6Å, and each of i and j is independently 0 or 1; Z^3 is NR or O; and each R is independently hydrogen or a noninterfering substituent~~.

54. (canceled)

55. (original): The composition of claim 53 which further contains an additional therapeutic agent.

56. (original): The composition of claim 55 wherein said additional therapeutic agent is a corticosteroid, a monoclonal antibody, or an inhibitor of cell division.

57. (currently amended): A method to treat a condition mediated by p38-α kinase comprising administering to a subject in need of such treatment a compound of claim 1 ~~the formula:~~



and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein

Ar^1 is an aryl group substituted with 0-5 non-interfering substituents, wherein two adjacent noninterfering substituents can form a fused aromatic or nonaromatic ring;

L^1 and L^2 are linkers;

each R^1 is independently a noninterfering substituent;

Z^1 is CR^2 or N wherein R^2 is hydrogen or a noninterfering substituent;

m is 0-4;

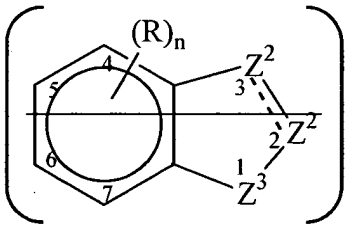
each of n and p is an integer from 0-2 wherein the sum of n and p is 0-3;

Ar^2 is a substantially planar, monocyclic or polycyclic aromatic moiety having one or more optional ring heteroatoms, said moiety being optionally substituted with one or more non-interfering substituents, two or more of which may form a fused ring;

Z is $-W_i-COX_jY$ wherein Y is COR^3 or an isostere thereof; R^3 is a noninterfering substituent, each of W and X is a spacer of 2-6 Å, and each of i and j is independently 0 or 1;

wherein the smallest number of covalent bonds in the compound separating the atom of Ar^1 bonded to L^2 to the atom of Ar^2 bonded to L^1 is at least 6, where each of said bonds has a bond length of 1.2 to 2.0 angstroms; and/or wherein the distance in space between the atom of Ar^1 bonded to L^2 and the atom of Ar^2 bonded to L^1 is 4.5-24 angstroms;

with the proviso that the portion of the compound represented by Ar^2-Z is not



wherein ⫽ represents a single or double bond; n is 0-3; one Z^2 is CA or CRA and the other is CR, CR_2, NR or N; A is $-W_i-COX_jY$ wherein Y is COR or an isostere thereof, each of W and X is a spacer of 2-6Å, and each of i and j is independently 0 or 1; Z^3 is NR or O; and each R is independently hydrogen or a noninterfering substituent.

58. (canceled)

59. (original): The method of claim 57 wherein said condition is a proinflammation response.

60. (currently amended): The method of claim 59 wherein said proinflammation response is multiple sclerosis, IBD, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, other arthritic conditions, sepsis, ~~septic shock,~~ endotoxic shock, ~~Gram-negative sepsis, toxic shock syndrome,~~ asthma, adult respiratory distress syndrome, **[[**~~stroke,~~**]]** reperfusion injury, ~~CNS injury,~~ psoriasis, ~~restenosis,~~ cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, a bone resorption disease, graft-versus-host reaction, Crohn's Disease, ulcerative colitis, ~~Alzheimer's,~~ or pyresis ~~or heart disease~~.